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(54) Title of Invention

A novel triazole derivative

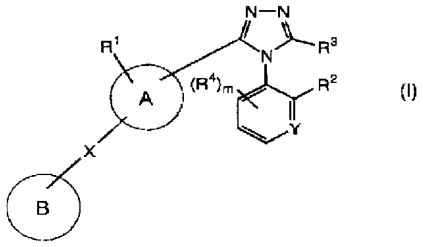
(57) Abstract

Subject

To put forward a V1 action inhibitor of arginine vasopressin with improved pharmacokinetics and high V1 receptor affinity.

Method of Solution

A triazole derivative represented by the general formula (I) or a pharmacologically acceptable salt thereof.



(I)

(wherein in the formula, Ring A denotes a benzene ring and the like, R^1 denotes a hydrogen atom, halogen atom or lower alkyl group and the like, the group represented by formula -X-B denotes a

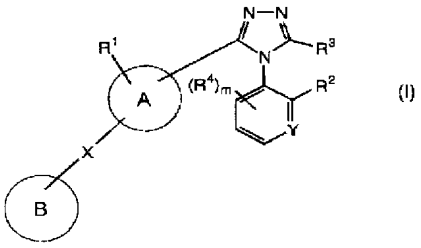
substituent that may be present when R^1 is hydrogen atom or lower alkyl group, and denotes a phenyl group and the like substituted by a heterocycle or a biphenyl, Y denotes N or CH, R^2 denotes an optionally substituted lower alkyl group or an optionally substituted alkoxyl group, R^3 denotes a lower alkyl group and the like, and R^4 denotes a hydrogen atom and the like)

(*Translator's note : the definition for the group -X-B here conflicts with the definition for Ring B in the Claims*)

Patent Claims

Claim 1

A drug containing a triazole derivative represented by following general formula (I) or a pharmaceutically acceptable salt thereof



(I)

(wherein, the symbols in the formula have the following definitions:

Ring A: a benzene ring or a thiophene ring,

R^1: a hydrogen atom, a halogen atom, a nitro group, an amino group or a lower alkyl group,

Group represented by formula -X-B: a substituent which may be present when R^1 denotes a hydrogen atom or a lower alkyl group, wherein the following definitions apply,

X: single bond, oxygen atom, -NHCO- group, -NHCONH- group, -NHCSNH- group or $-(CH_2)_n-O-$ group (n denotes an integer of 1-5),

Ring B: an aryl group which may be substituted by a lower alkyl group or a phenyl group or alternatively a heterocyclic group which may be substituted by a lower alkyl group,

Y: N or CH,

R^2: an optionally substituted lower alkyl group, a halogen atom, a hydroxyl group, a phenyl group, an optionally substituted alkoxyl group, an optionally substituted lower alkynyl group or an optionally substituted amino group,

R^3: a hydrogen atom or a lower alkyl group,

R^4: a lower alkyl group, a lower alkoxyl group, a lower alkyl sulphonyl group, a halogen atom, an amino group, a cyano group, a trihalogenomethyl group, a nitro group or a group which may form a cycloalkyl group together with R^2, and moreover,

m denotes 0 or an integer of 1-3).

Claim 2

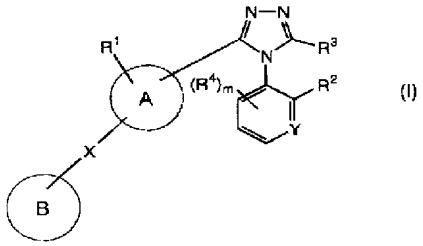
A V1 receptor antagonist of arginine vasopressin containing a triazole derivative in accordance with Claim 1 or a pharmaceutically acceptable salt thereof.

Claim 3

A therapeutic agent for diabetic nephropathy containing a triazole derivative in accordance with Claim 1 or a pharmaceutically acceptable salt thereof.

Claim 4

A triazole derivative represented by the following general formula (I) or a pharmaceutically acceptable salt thereof.



(I)

(wherein, the symbols in the formula have the following definitions:

Ring A: a benzene ring or a thiophene ring,

R^1: a hydrogen atom, a halogen atom, a nitro group, an amino group or a lower alkyl group,

Group represented by formula -X-B: a substituent which may be present when R^1 denotes a hydrogen atom or a lower alkyl group, wherein the following definitions apply,

X: single bond, oxygen atom, -NHCO- group, -NHCONH- group, -NHCSNH- group or $-(CH_2)_n-O-$ group (n denotes an integer of 1-5),

Ring B: a heterocyclic group which may be substituted by a lower alkyl group or an aryl group which may be substituted by a phenyl group or a lower alkyl group,

Y: N or CH,

R^2: a hydrogen atom, an optionally substituted lower alkyl group, a halogen atom, a hydroxyl group, a phenyl group, an optionally substituted alkoxyl group (wherein when the group represented by formula -X-B denotes an unsubstituted 4-biphenyl group, Y denotes CH and R^3 denotes a methyl group, then R^2 denotes a group other than methoxy), an optionally substituted lower alkynyl group or an optionally substituted amino group,

R^3: a hydrogen atom or a lower alkyl group,

R^4: a lower alkyl group, a hydroxyl group, a lower alkoxyl group, a lower alkyl sulphonyl group, a halogen atom, an amino group, a cyano group, a trihalogenomethyl group, a nitro group or a group which may form a cycloalkyl group together with R^2, moreover,

m denotes 0 or an integer of 1-3).

Detailed Description of the Invention

(0001)

Technical Sphere of this Invention

This invention relates to a drug, and more particularly to a novel triazole derivative that antagonises the V1 receptor of arginine vasopressin or a pharmacologically acceptable salt thereof and a V1 receptor antagonist of arginine vasopressin containing these as an effective component.

(0002)

Technology of the Prior Art

Diabetic nephropathy is one of three major complications of diabetes mellitus, and metabolic abnormalities centring around hyperglycemia are deeply involved in the onset development thereof. Early diagnosis has now become possible by diagnosis of trace albuminuria before the onset of proteinuria, and there is increasing demand as regard the prevention and therapy of early stage diabetic nephropathy.

(0003)

In diabetic patients and diabetes mellitus model animals, a rise in arginine vasopressin (hereinafter, abbreviated to AVP) concentration in plasma is observed, suggesting the participation of AVP in diabetes mellitus (Diabetes, 38 (1989), 54-57). AVP, a peptide comprising nine amino acids, is biosynthesised and

secreted by the hypothalamus-pituitary system and known AVP receptors comprise V1 and V2 receptors. More particularly, V1 receptors are known, to be involved in the contraction of the efferent arteriole (Am. J. Physiol. 256 [1989] F274-F278) and the synthesis of prostaglandin E2 species (J. Hypertension 11 [1993] 127-134), to cause increases in glomerula addition, and to be involved in the proliferating action of mesangial cells due to AVP. In addition, it has been made clear that V1 receptors are deeply involved in the onset and aggravation of diabetic nephropathy. Furthermore, there is a clinical report that OPC-21268 (the compound of Example 141 in EP 382185), a V1 selective antagonist, improved NIDDM patient albuminuria. Therefore, V1 antagonists may be expected to become effective preventative • therapeutic agents for early diabetic nephropathy.

(0004)

Moreover, vasopressin has recently been shown to strongly promote the production of vascular permeability facilitation factor (VPF) and/or vascular endothelial growth factor (VEGF) through V1 receptors, and therefore an involvement in the formation process of blood vessel lesions in various types of diseases such as diabetic retinopathy, diabetic nephropathy, arteriosclerosis or the like has been suggested (Biochimica et Biophysica Acta 1243 [1995] 195-202). Accordingly, V1 antagonists are useful for the prevention and treatment of vascular ailments in various diseases.

(0005)

On the other hand, V2 receptor antagonists are known to have a water diuretic action and compounds that antagonise both V1 and V2 receptors are preferred in renal disease accompanied by edema. As such compounds, for example benzazepine derivatives as described in International Laid-Open Patent Applications WO 95/03305 and WO 95/06035 are known. However, V1 receptor selective antagonists are more preferred for diseases that are unaccompanied by edema, for example, early diabetic nephropathy showing symptoms of a dry mouth, polyuria or the like.

(0006)

Oxytocin is known as a peptide, made of nine amino acids, which is extremely analogous to AVP and is biosynthesised and secreted by the hypothalamus-pituitary system. Some species of AVP antagonist are known to antagonise oxytocin receptors and to cause an inhibiting action on uterine contraction, milk ejection and the like.

(0007)

Accordingly, compounds which are selective to and have a stronger antagonism for V1 receptors as compared to V2 receptors and oxytocin receptors are currently expected to be good therapeutic agents for diseases involving V1 receptors unaccompanied by edema, such as blood vessel ailments in various diseases or early diabetic nephropathy.

(0008)

Problems to be Overcome by this Invention

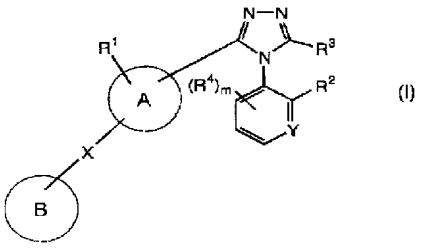
On the basis of the background as described above, these inventors carried out screening for compounds having selective and high V1 receptor affinity, and as a result discovered that a certain species of specific triazole derivatives satisfied the aforesaid requirements. This invention was completed on the basis of this discovery.

(0009)

Means to Overcome these Problems

This invention relates to a triazole derivative represented by following general formula (I) or a pharmacologically acceptable salt thereof

(0010)



(I)

(0011)

(wherein in the formula, the symbols have the following meanings.

Ring A: a benzene ring or a thiophene ring,

R^1: a hydrogen atom, a halogen atom, a nitro group, an amino group or a lower alkyl group,

Group represented by formula -X-B: a substituent which may be present when R^1 denotes a hydrogen atom or a lower alkyl group, wherein the following definitions apply,

X: single bond, oxygen atom, -NHCO- group, -NHCONH- group, -NHCSNH- group or $-(CH_2)_n-O-$ group (n denotes an integer of 1-5),

Ring B: a heterocyclic group which may be substituted by a lower alkyl group or an aryl group which may be substituted by a phenyl group or a lower alkyl group, Y: N or CH,

R^2: a hydrogen atom, an optionally substituted lower alkyl group, a halogen atom, a hydroxyl group, a phenyl group, an optionally substituted alkoxyl group, an optionally substituted lower alkynyl group or an optionally substituted amino group,

R^3: a hydrogen atom or a lower alkyl group,

R^4: a lower alkyl group, a hydroxyl group, a lower alkoxyl group, a lower alkyl sulphonyl group, a halogen atom, an amino group, a cyano group, a trihalogenomethyl group, a nitro group or a group which may form a cycloalkyl group together with R^2, and moreover,

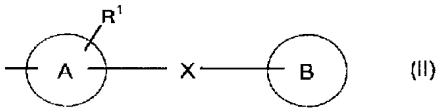
m denotes 0 or an integer of 1-3).

(0012)

Conditions for carrying out this invention

The triazole derivatives in accordance with this invention will now be described in greater detail. Among the triazole derivatives in accordance with this invention, when Ring A is a benzene ring, compounds are preferred wherein in substituent -X-B which may be present when R^1 comprises hydrogen or lower alkyl, X is single bond and Ring B is an unsubstituted aryl group and in particular a phenyl group; namely compounds are preferred wherein the substituent at the 3-position of the triazole ring represented by formula (II)

(0013)



(II)

(0014)

(wherein in the formula, Ring A, Ring B, R^1 and X each have the same aforesaid meanings), is a biphenyl group, more particularly a 4-biphenyl group.

(0015)

Furthermore, when the substituent at the 3-position is a biphenyl group, as the substituent at the 4-position of the triazole ring, a phenyl group wherein Y is CH is preferred, and among such compounds, the species wherein R^2 of the same substituent is an optionally substituted alkoxyl group is preferred. In particular a species wherein the carbon number of the alkoxyl group is 2-10 and a heterocycle is bonded to the terminal carbon atom is preferred. Examples of such heterocycles include 4-substituted piperidino groups, substituted piperidyl groups, 4-substituted piperazinyl groups, substituted homopiperazinyl groups, substituted azepanyl groups, morpholino groups and the like.

(0016)

Of course, among the compounds in accordance with this invention, the aforesaid description only outlines examples of those compounds wherein the substituent represented by aforesaid formula (II) is a biphenyl group. Accordingly this said description does not include all the compounds in accordance with this invention and does not necessarily list all preferred compounds.

(0017)

Moreover, the term "lower" in this specification denotes a straight chain or branched form hydrocarbon chain of carbon number 1-6.

(0018)

Accordingly, examples of "lower alkyl group" include a methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, iso pentyl group and the like.

(0019)

Examples of "lower alkoxyl group" include a methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, hexyloxy group, iso hexyloxy group and the like. Moreover, examples of "alkoxyl group" include alkoxyl groups of carbon number up to 12, and in addition to the aforesaid lower alkoxyl groups include a heptanoxy group, octanoxy group, nonanoxy group, decanoxy group, undecanoxy group, dodecanoxy group and branched alkoxyl groups having the same carbon numbers as these.

(0020)

Examples of "halogen atom" include fluorine atom, chlorine atom, bromine atom and iodine atom.

(0021)

The "heterocyclic group" for the Ring B group includes nitrogen-containing aromatic 5 to 6 membered heterocyclic groups such as a pyrrolyl group, pyrrolinyl group, imidazolyl group, pyrazonyl group, pyrazolyl group, pyrrolidinyl group, furyl group (sic), pyridyl group, pyrazinyl group, piperidyl group, pyrimidinyl group, pyridazinyl group, pyrrolidinyl group, tetrazolyl group, triazolyl group, thiazolyl group, oxazolyl group and the like, and furthermore nitrogen-containing saturated 5 to 8 membered heterocyclic groups such as a piperidino group, piperidyl group, morpholino group, morpholinyl group, piperazinyl group, imidazolyl group, homopiperazinyl group and the like.

(0022)

Examples of "lower alkynyl group" include alkynyl groups of carbon number 2-6, such as an ethynyl group, 1-propynyl group, 2-propynyl group, 1-butynyl group, 2-butynyl group, 3-butynyl group, 1-methyl-2-propynyl group, 1-pentynyl group, 2-pentynyl group, 3-pentynyl group, 4-pentynyl group, 3-methyl-1-butynyl group, 2-methyl-3-butynyl group, 1-methyl-2-butynyl group, 1-methyl-3-butynyl group, 1,1-dimethyl-2-propynyl group, 1-hexynyl group, 2-hexynyl group, 3-hexynyl group, 4-hexynyl group, 5-hexynyl group and the like. Examples of the substituent of "lower alkynyl group" include in addition to a hydroxy group, halogen atom or the like, "an optionally substituted alkoxyl group" as described in detail below.

(0023)

The substituent of the "optionally substituted alkoxyl group", may be an aforesaid heterocycle wherein the said heterocycle may itself be substituted by a heterocycle or lower alkyl group. Furthermore, an optionally substituted phenyl group may be included. Examples of the substituent of the aforesaid phenyl group include 4-lower alkyl piperazinyl carbonyls and the like. Examples of such "optionally substituted alkoxyl group" include the following groups. Namely, examples include a phenyl alkoxy group, (4-alkyl piperazin-1-yl carbonyl) phenylalkoxy group, (4-piperidino piperidino carbonyl) phenyl alkoxy group, (piperidinocarbonyl) phenyl alkoxy group, (4-alkyl piperazin-1-yl carbonyl) alkoxy group, (4-piperidino piperidino carbonyl) alkoxy group, (piperidino carbonyl) alkoxy group, (morpholino carbonyl) alkoxy group, (alkoxy carbonyl) alkoxy group, (hydroxy carbonyl) alkoxy

group, [(4-alkyl piperazin-1yl) alkylamino carbonyl] alkoxy group, [4-(pyrimidin-2-yl) piperazin-1yl] alkoxy group, [4-(2-pyridyl) piperazin-1-yl] alkoxy group, (4-alkyl piperazin-1-yl) alkoxy group, (4-alkyl homopiperazin-1-yl) alkoxy group, (4-piperidino piperidino) alkoxy group, [(piperidinyl-1-yl) alkylamino] alkoxy group, piperidino alkoxy group, piperidyl alkoxy group, morpholino alkoxy group, pyridyl alkoxy group, imidazolyl alkoxy group, (2-aminophenoxy) alkoxy group, hydroxy alkoxy group and the like.

(0024)

The "optionally substituted amino group" may be an amino group substituted by a lower alkyl group, namely a straight chain or branched alkyl group of carbon number 1-6. Moreover, a nitrogen atom-containing heterocycle may be formed together with another substituent. Examples of such heterocycles include the aforesaid heterocycles exemplified for Ring B. Moreover, these heterocycles may also have substituents, and as amino groups having such a substituent, species in which a lower alkyl group or acid residue such as acetic acid, propionic acid and the like is bonded to the nitrogen atom at the 4 position of the heterocycle are included.

(0025)

Examples of cycloalkyl groups formed from R^2 and R^4 bonded in the ortho position, include a cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclo octyl group and the like.

(0026)

When Ring A is a phenyl group, examples of substituents constructed from the said ring and formula -X-B include the following. Namely, a phenoxy phenyl group, phenyl alkoxy phenyl group, (2-biphenyl) carbonylamino phenyl group, optionally lower alkyl - substituted biphenyl group, optionally lower alkyl - substituted furyl carbonylamino phenyl group, biphenyl group, piperidino phenyl group, (piperidino alkoxy) phenyl group, optionally lower alkyl - substituted pyrrolidinyl phenyl group, optionally lower alkyl - substituted imidazolyl phenyl group, optionally lower alkyl - substituted thiazolyl phenyl group, morpholino phenyl group, (morpholino alkoxy) phenyl group, optionally lower alkyl - substituted phenyl ureylene phenyl group, optionally lower alkyl - substituted phenyl thioureylene phenyl group, phenoxy phenyl group, phenyl thiophenyl group and the like.

(0027)

The "aryl group" is preferably an aryl group of carbon number 6-14, and examples include a phenyl group, biphenyl group, naphthyl group, anthryl group, phenanthryl group and the like.

(0028)

The compounds of this invention, in some cases, form salts with inorganic acids or organic acids, and the salts thereof also have a V1 action inhibitory effect. Ideal salts include for example salts with mineral acids such as of hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid and the like, salts with organic acids such as of formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, carbonic acid, glutamic acid, aspartic acid, methanesulphonic acid, ethanesulphonic acid and the like, salts with inorganic bases such as of sodium, potassium, magnesium, calcium, aluminium and the like, salts with organic bases such as of methylamine, ethylamine, ethanolamine and the like, and salts with basic amino acids such as of lysine, ornithine and the like. Moreover, quaternary ammonium salts can be formed by reaction with a lower alkyl halide, lower alkyl triflate, lower alkyl tosylate or benzyl halide and the like, however as quaternary ammonium salt, a salt with methyl iodide or benzyl chloride or the like is preferred.

(0029)

In some cases with the compounds of this invention, optical isomers are present based on an asymmetric carbon atom and geometric isomers are present based on a double bond or cyclohexane ring. In addition, when a compound has two or more asymmetric carbon atoms, diastereoisomers are also present. Isolated species of these various isomers and mixture of these isomers are included in this invention. Moreover hydrates, various solvates and tautomers and the like are included in the compounds of this invention. Furthermore the compounds of this invention also include compounds having crystalline polymorphism, and all of their crystalline forms are included in the compounds of this invention.

(0030)

The compounds which are the effective components of the drug in accordance with this invention are novel other than the case wherein in general formula (I), the substituent constructed from Ring A and

formula -X-B is an unsubstituted 4-biphenyl group, R^3 is a methyl group, R^4 is a hydrogen atom, Y is CH and R^2 is methoxy group. The species of general formula (I), wherein the substituent constructed from Ring A and formula -X-B is an unsubstituted 4-biphenyl group, R^3 is a methyl group, R^4 is a hydrogen atom, Y is CH and R^2 is a methoxy group has been synthesised by Labotest AG. (Freiburg, Germany), and is available on request from Labotest AG.

(0031)

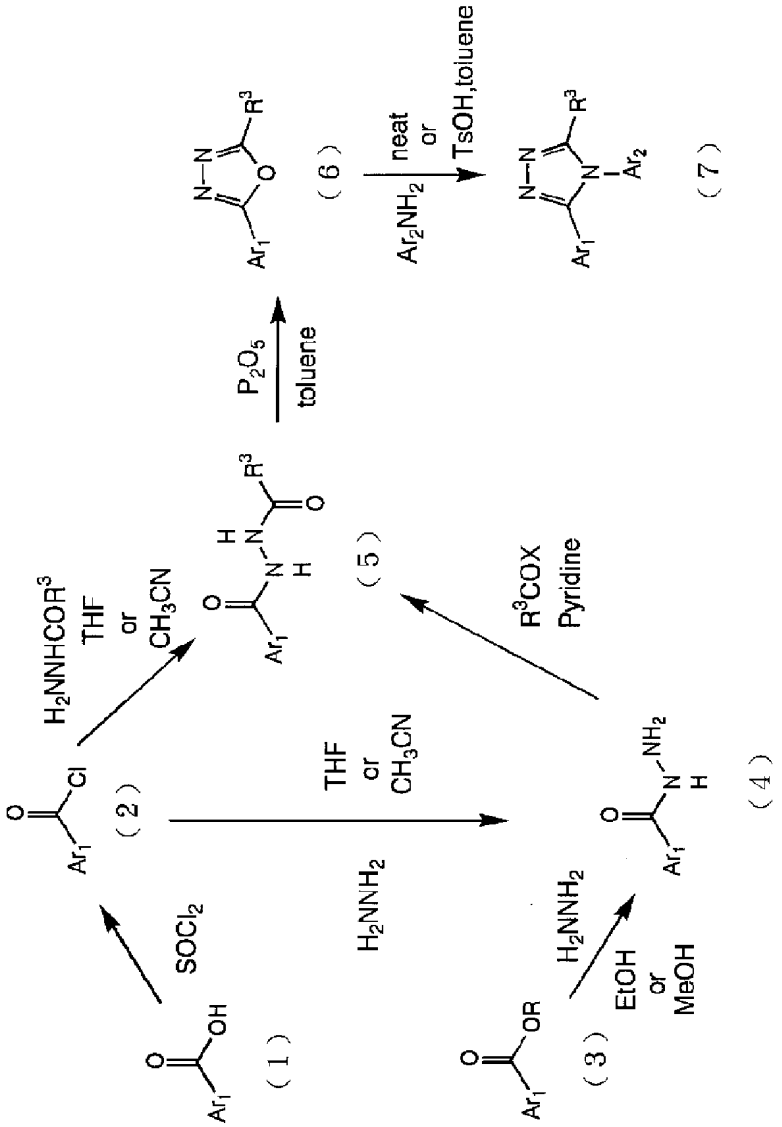
Processes for Production

Processes for the production of compounds in accordance with this invention will now be described. The basic backbone, namely 3,4-diaryl substituted-5-substituted-1,2,4-triazole derivatives (7) can be usually produced by the two methods described below. First of all, in the first method, as illustrated by the following Reaction Scheme 5, an aromatic carboxylic acid (1) activated using thionyl chloride to the aromatic carboxylic acid chloride is condensed in an inert solvent such as tetrahydrofuran, acetonitrile or the like, or, an acid hydrazide (4) obtained by reacting an aromatic carboxylic acid ester with 10 equivalents of hydrazine in alcohol, is condensed in the presence of an acylating agent such as acetic anhydride and the like and organic base such as pyridine and the like, or, the aromatic carboxylic acid chloride (2) is directly reacted with acid hydrazide and thereby diacyl hydrazine (5) is obtained, then the diacyl hydrazine (5) obtained in this way is subjected to a cyclisation reaction in the presence of a dehydrating agent such as phosphorous pentoxide or the like, and a 1,3,4-oxazole (6) thereby obtained, and this is heated with an aniline derivative in the absence of solvent or heated under reflux in an solvent such as toluene and the like in the presence of an acid catalyst such as tosylic acid and the like, and the target 1,2,4-triazol derivative (7) thereby obtained.

(Translator's note :The Japanese here seems grammatically flawed and reference needs to be made to the Reaction Scheme to get a clear understanding of the meaning)

(0032)

Reaction Scheme 5



(0033)

Moreover, a process for the production of diacyl hydrazine (5) has been described by E. Klinsberg, (J. Am. Chem. Soc., 1958, 80, 5786-5789), and this description may be referred to in accordance with requirements. Moreover, as acid catalyst used during the heating under reflux, mesylic acid, camphor

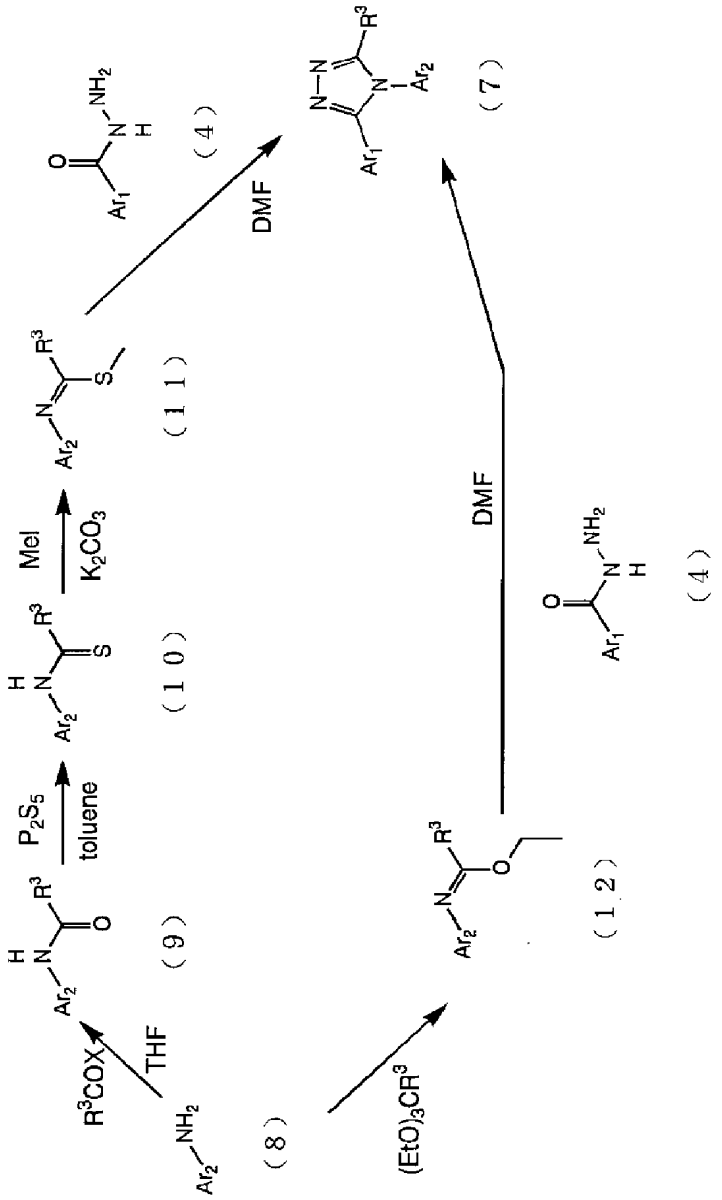
sulphonic acid and the like can be used in addition to tosylic acid, while as solvent, xylene, mono- or di-chlorobenzene and the like can be used in addition to toluene.

(0034)

As the second method, as shown in the following Reaction Scheme 6, an aniline derivative (8) is condensed with an acylating agent such as acetic anhydride and the like in an organic solvent such as tetrahydrofuran or the like and thereby an anilide (9) is obtained. This is thioamidated using phosphorus pentasulphide or the like in an organic solvent such as toluene and a thioamide (10) thereby obtained, The thioamide (10) obtained in this way is converted to the S-methylthio imidate (11) with methyl iodide, and this is heated and reacted at 120°C with acid hydrazide (4) and dimethyl formaldehyde (hereinafter, abbreviated to DMF) and the 1,2,4-triazole derivative (7) thereby obtained. Alternatively, compound (8) is heated with an ortho acid ester, thereby an o-alkylimidate (12) formed, and this is reacted with acid hydrazide (4) in the same way as above and the 1,2,4-triazole derivative (7) thereby obtained. In the reaction with the acid hydrazide (4), as solvent, in addition to DMF, dimethylacetamide, DMSO, 1-methyl-2-pyrolidone and the like are ideally used.

(0035)

Reaction Scheme 6



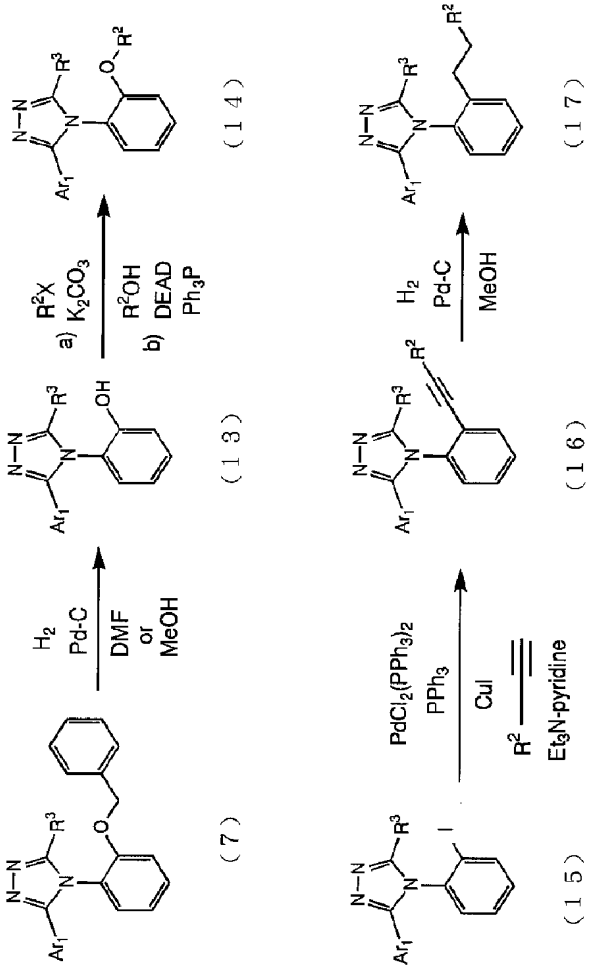
(0036)

Next, a conversion method for the side chains such as R^2 or the like will be described. The methods illustrated in the following Reaction Scheme 6 (sic) may be nominated as conversion methods for the side chains. Namely, a benzyloxy derivative (7) may be debenzylated by a catalytic reduction and thereby

a phenol derivative compound (13) obtained, and an alkyl group is introduced onto this by a Mitsunobu reaction with an alkyl halide, alkyl sulphonate or alcohol, and thereby an alkyloxyphenyl triazole derivative (14) obtained. Moreover, the phenol derivative compound (13) may be reacted with an alkylene dihalide, thereby forming a halogeno alkyloxyphenyl triazole derivative and this subject to a substitutional reaction with an amine, and thereby an aminoalkoxy phenyl triazole derivative obtained. Moreover, an iodine compound (15) may be subject to a Sonogashira reaction ($PdCl_2$ $(PPh_3)_2$, CuI, PPh_3, acetylene / Et_3N-pyridine) and thereby an alkylene derivative (16) obtained, and this subjected to a catalytic reduction and thereby an alkylphenyl triazole derivative (17) obtained.

(0037)

Reaction Scheme 7



(0038)

Moreover, as described above, in the compounds of this invention, isomers such as racemates, optically active forms, diastereomers and the like may be present singly or as mixtures thereof. A racemate can be derived by using a suitable starting material compound, or a stereochemically pure isomer can be derived by an ordinary racemic resolution method (for example, a method wherein optical resolution is carried out by deriving a diastereomeric salt using an ordinary optically active acid [tartaric acid or the like]). Moreover, a mixture of diastereomers can be separated by a conventional method, for example by fractional crystallisation or chromatography and the like.

(0039)

Advantages Afforded by this Invention.

The compounds of this invention selectively antagonise the V1 receptors for AVP in preference to the V2 receptors for AVP and oxytocin receptors, and therefore have for example a vasodilating action, blood pressure depressing action, cardiac function facilitating action, myocardial cell hypertrophy inhibitory action, vascular smooth muscle proliferation • hypertrophy inhibitory action, mesangial cell proliferation • hypertrophy inhibitory action, mesangial cell contraction inhibitory action, platelet aggregation inhibitory action, vascular permeability facilitation factor (VPF) • neovascularization factor (VEGE) production inhibitory action, endothelin production inhibitory action, liver gluconeogenesis inhibitory action and the like.

(0040)

Moreover, because the action of the compounds of this invention with respect to AVP is V1 receptor selective, the action is not accompanied by a water diuretic action on the basis of V2 receptor antagonism or actions such as uterine contraction or the like on the basis of oxytocin receptor antagonism. Therefore the compounds of this invention can be used for the treatment of various diseases in which the V1 receptor of AVP is involved, and the said compounds are useful as for example vasodilators, antihypertensive drugs, anti-cardiac insufficiency agents, anti-renal failure agents, platelet aggregation depressants and the like, and are useful for the prevention and treatment of hypertension, cardiac incompetency, nephropathy, cerebrovascular disorder, diabetes, diabetic nephropathy, diabetic retinopathy, various ischemic diseases, circulatory failure, arterial sclerosis, gastric ulcer, nausea, vomition, absentia, malignant carcinoma, renal function failure and the like. In particular, the

compounds of this invention are useful for the prevention and treatment of early diabetic nephropathy. Moreover, the compounds of this invention have excellent oral absorptivity, and in addition are likely to be metabolised in-vivo with difficulty and have a good sustained effect.

(0041)

The pharmacological action of the compounds of this invention will now be illustrated using a Test Example.

(0042)

V1 antagonism in unanesthetised rat (oral administration).

The V1 antagonism was examined using male Wistar rats (300-320 g in weight) in which a cannula for sphygmomanometry had been inserted into the left carotid artery and a cannula for AVP administration had been inserted into the left jugular vein two or three days before the start of the experiment. The blood pressure was measured without anesthesia from the arterial cannula via a pressure transducer. The test compound was suspended in 0.5 % methyl cellulose solution and was orally-administered with dosages of 1, 10 and 100 mg/kg.

(0043)

The increase in diastolic blood pressure due to the intravenous administration of 30 mU/kg AVP before the test compound administration was designated as being 100 %, and the pressure increase due to the intravenous administration of 30 mU/kg AVP was regularly measured from 30 minutes to 8 hours after the administration of the test compound. The rate of inhibition of the pressure increase due to the test compound was determined, and the V1 antagonism of the test compound was assessed. As a result, the compound of this invention showed a potent and sustained V1 antagonism.

(*Translator's note : Neither the specific compound used in the test or the actual test results are specified in this patent application*).

(0044)

Medicinal compositions containing as effective component, one or more of the compounds represented by general formula (I) and pharmacologically acceptable salts or hydrates thereof and the like can be administered orally or aorally, and such compositions can be prepared as tablets, powders, fine

granules, granules, capsule agents, pills, liquid medicines, injections, suppositories, ointments, patches and the like using conventional carriers, excipients and other additives used for formulations.

(0045)

The clinical dosage of the compound of this invention to man is suitably determined on the basis of the individual patient on consideration of the patient's symptoms, age, sex, body weight or the like, but usually the oral dose is 0.1-500 mg per adult per day, and the said dose is administered once or is divided several times. In addition, because the dosage will vary according to various conditions, there may situations wherein a quantity lower than the aforesaid dosage range may be sufficient.

(0046)

As solid compositions for oral administration in accordance with this invention, tablets, powders, granules and the like may be used. In such solid compositions, one or more active materials are mixed with at least one inert diluent, for example, lactose, mannitol, dextrose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate or the like.

(0047)

In accordance with conventional methods, the composition may contain additives other than an inert diluent, for example, a lubricant such as magnesium stearate, a disintegrating agent such as calcium carboxymethyl cellulose, a stabilising agent such as lactose, and a solubiliser or solubilising agent such as glutamic acid or aspartic acid. A tablet or pill may be coated in accordance with requirements with sucrose, or a film of a stomach-soluble or enteric-soluble substance such as gelatin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate or the like. Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixir agents, and may contain generally used inert diluents, for example purified water and ethanol. Such compositions may contain solubilising agents or solubilisers, wetting agents and adjuvants such as suspending agents, sweeteners, flavor agents, aromatics and preservatives in addition to inert diluent.

(0048)

Injection agents for aoral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Diluents for aqueous solutions and suspensions include for example distilled

water for injection and physiological saline. Examples of water insoluble solvents and suspending agents include for example propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol and detergents such as Polysorbate 80 (Trade name) and the like. Furthermore such compositions may also contain an isotonising agent, preservative, wetting agent, emulsifier, dispersant, stabilising agent (for example lactose) and solubilising agent or solubiliser (for example glutamic acid or aspartic acid). They are sterilised for example by filtration through a bacteria retaining filter, formulation of antimicrobial agent or irradiation. Alternatively, they can be produced as a sterile solid composition which is used by dissolution in sterile water or a sterile injectable solvent before use.

(0049)

Examples

This invention will now be described in greater detail by reference to Examples. Needless to say but this invention is not restricted just to the compounds of the Examples. Furthermore, when a starting material used in this invention is novel, such a compound will be illustrated using a Reference Examples.

(0050)

Example 1

4-(2-methoxyphenyl)-3-(4'-biphenyl)-1,2,4-triazole (Compound number 22)

A mixture of 538 mg 3-(4'-biphenyl)-1,3,4-oxadiazole and 6 ml o-anisidine was heated in the absence of solvent at 150°C for 12 hours. The reaction mixture was refined by silica gel column chromatography, and thereby 95 mg of the title compound representing a yield of 12 % was obtained as a brown solid. The NMR data of the obtained compound was as follows.

3.63 (3H, s), 7.11 (1H, t, J = 7.5 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.35-7.57 (7H, m), 7.67-7.69 (4H, m), 8.72 (1H, s).

(0051)

Reference Example 1

N-(2-benzyloxyphenyl) acetamide

To a 100 ml ethyl acetate solution of 10.91 g of 2-aminophenol was added 20 ml acetic anhydride at room temperature and the mixture stirred for 30 minutes. The reaction liquor was concentrated, and thereafter ethyl acetate was added to the residue and the crystals recovered by filtration. A 300 ml

acetonitrile liquid mixture of the said crystals, 18.8 g benzyl bromide and 30.0 g potassium carbonate was stirred at 70°C overnight. The reaction liquor was filtered and thereafter ethyl acetate was added to the residue, and this mixture was washed with water and saturated aqueous sodium chloride solution, dried, and thereafter concentrated. The residue was refined by silica gel column chromatography, and the 22.64 g of the title compound thereby obtained as a white solid represented a yield of 94 %. The physical properties of this compound were as follows.

FAB-MS m/z: 242 (M^+ + H). ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 5.12 (2H, s), 6.92-7.05 (3H, m), 7.35-7.48 (5H, m), 7.76 (1H, br s), 8.30-8.40 (1H, m).

(0052)

Reference Example 2

N-(2-benzyloxyphenyl)-S-methyl acetothioimidate

A 300 ml toluene liquid mixture of 22.55 g of N-(2-benzyloxyphenyl) acetamide and 23.0 g phosphorus pentasulphide was stirred at 70°C for two hours. The supernatant fraction of the reaction liquor was separated and thereafter concentrated, and the residue was refined by silica gel column chromatography and 11.51 g of N-(2-benzyloxyphenyl) thioacetamide was thereby obtained as a brown liquid. A 300 ml acetonitrile liquid mixture of this liquid, 20.0 g methyl iodide and 30.0 g potassium carbonate was stirred at 50°C for three hours. The reaction liquor was filtered, ethyl acetate was added to the residue, and this mixture was washed with water and saturated aqueous sodium chloride solution and concentrated after drying. The residue was refined by silica gel column chromatography, and the 16.23 g of the title compound thereby obtained as a red liquid represented a yield of 64 %. The physical properties of this compound were as follows.

FAB-MS m/z: 272 (M^++H). ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, s), 2.46 (3H, s), 4.99 (2H, s), 6.65 (1H, d, J = 10Hz), 6.90-7.08 (3H, m), 7.28-7.49 (5H, m).

(0053)

Reference Example 3

Biphenyl-4-carboxylic acid hydrazide

A 100 ml ethanol liquid mixture of 2.26 g biphenyl-4-carboxylic acid ethyl ester and 5.0 g hydrazine • monohydrate was stirred overnight at 170°C in a sealed tube container. The reaction liquor was concentrated, ethyl acetate was added, and thereafter the crystals were recovered by filtration and

the 1.59 g of the title compound thereby obtained as a white solid represented a yield of 75 %. The physical properties of this compound were as follows.

FAB-MS m/z: 213 (M^++H). ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, br s), 7.30-7.60 (3H, m), 7.60-7.90 (4H, m), 7.90-8.00 (2H, m), 9.83 (1H, br s).

(0054)

Example 2

4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound number 39)

A 3 ml dimethylformamide (DMF) solution of 300 mg N-(2-benzyloxyphenyl)-S-methyl acetothioimidate and 212 mg of 4-biphenylcarboxylic acid hydrazide was stirred at 120°C for two hours. The reaction liquor was filtered, ethyl acetate was added to the residue, and this mixture was washed with water and saturated aqueous sodium chloride solution, dried and thereafter concentration was carried out. The residue was refined by silica gel column chromatography and crystallised from hexane - ethyl acetate, and the 275 mg of the title compound thereby obtained as a white solid represented a yield of 66%. The NMR data of this compound was as follows.

2.31 (3H, s), 4.95 (1H, d, J = 13Hz), 5.06 (1H, d, J = 13Hz), 6.95-7.15 (4H, m), 7.20-7.60 (14H, m) / $CDCl_3$.

(0055)

Example 3

2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol (Compound number 43)

A 50 ml DMF liquid mixture of 2.78 g of 4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole and 0.50 g of 10 % palladium-carbon was stirred overnight at room temperature. The reaction liquid was filtered while warm, and after concentrating, ethyl acetate was added to the residue. The crystals were recovered by filtration, and thereby 2.05 g of the title compound was obtained as a grey solid. The NMR data of this compound was as follows.

2.17 (3H, s), 6.95 (1H, t, J = 8Hz), 7.07 (1H, t, J = 8Hz), 7.30-7.53 (7H, m), 7.60-7.65 (4H, m), 10.33 (1H, s) / DMSO-d_6.

(0056)

Reference Example 4

4-[2-(6-bromo hexyloxy) phenyl]-3-(4'-biphenyl)-5-methyl-1,2,4-triazole

A 50 ml acetonitrile liquid mixture of 1.04 g of 2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol, 3.90 g of 1,6-dibromohexane and 3.0 g potassium carbonate was stirred at 50°C for 30 minutes. The reaction liquor was filtered, ethyl acetate was added to the residue, and this mixture was washed with water and saturated aqueous sodium chloride solution, dried and thereafter concentrated. The residue was refined by silica gel column chromatography, and the 1.22 g of the title compound thereby obtained as an amorphous solid represented a yield of 77 %. The physical properties of this compound were as follows.

FAB-MS m/z: 492 (M^++H). ^{1}H-NMR ($CDCl_3$) δ: 1.15-1.35 (4H, m), 1.50-1.65 (2H, m), 1.68-1.90 (2H, m), 2.29 (3H, s), 3.31 (2H, t, J =7Hz), 3.75-3.99 (2H, m), 7.06 (2H, t, J = 8Hz), 7.15-7.60 (13H, m).

(0057)

Example 4

4-{2-[6-methylpiperazin-1-yl] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound number 54)

An acetonitrile (20 ml) liquid mixture of 0.60 g of 4-(2-(6-bromo hexyloxy) phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole, 200 mg of 1-methylpiperazine and 2.0 g potassium carbonate was stirred at 70°C for two hours. The reaction liquor was filtered and thereafter chloroform - methanol (10:1) was added to the residue, and this mixture was washed with water and saturated aqueous sodium chloride solution, dried and thereafter concentrated. The residue was refined by silica gel column chromatography and crystallised from hexane - ethyl acetate, and the 420 mg of title compound thereby obtained as a white solid represented a yield of 69%. The NMR data of this compound was as follows.

1.18-1.23 (4H, m), 1.35-1.44 (2H, m), 1.51-1.60 (2H, m), 2.22-2.30 (4H, m), 2.27 (3H, s), 2.29 (3H, s), 2.42 (6H, brs), 3.80-3.87 (1H, m), 3.91-3.98 (1H, m), 7.02-7.07 (2H, m), 7.17 (1H, dd, J = 1.7Hz, 7.7Hz), 7.31-7.56 (10H, m) / $CDCl_3$.

(0058)

Example 5

4-{2-[4-(4-piperidyl) butoxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound number 72)

A 10 ml acetonitrile liquid mixture of 440 mg of 2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol, 890 mg of 4-[4-(1-trityl) piperidyl] butyltoluene sulphonate and 2.0 g potassium carbonate was stirred at 80°C for three hours. The reaction liquor was filtered, and thereafter the filtrate was concentrated, the residue refined by silica gel column chromatography and 1.01 g (quant.) of the title substance N-trityl body was thereby obtained. Of this, 500 mg of the said body was deprotected in hydrochloric acid-ethanol-ethyl acetate and the 220 mg of title compound thereby obtained represented a yield of 67 %. The NMR data of this compound was as follows.

0.90-1.75 (11H, m), 2.30 (3H, s), 2.55-2.85 (2H, m), 3.00-3.25 (2H, m), 3.80-4.05 (2H, m), 7.10-7.80 (13H, m), 8.81 (1H, br), 9.05 (1H, br) / DMSO-d_6.

(0059)

Example 6

4-{2-[3-(3-pyridyl) propyl] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound number 85)

To a 5ml THF solution of 220 mg of 2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol, 140 mg of 3-(3-pyridyl) propanol and 310 mg triphenylphosphine was added 210 mg diethyl azodicarboxylate under ice cooling and the mixture stirred for 20 minutes. The reaction liquor was concentrated, and thereafter the residue was refined by silica gel column chromatography and crystallised from hexane - ethyl acetate. The 156 mg of the title compound thereby obtained as a white solid represented a yield of 52 %. The NMR data of this compound was as follows.

1.75-1.95 (2H, m), 2.32 (3H, s), 2.30-2.60 (2H m), 3.75-4.00 (2H, m), 6.95-7.60 (15H, m), 8.30 (1H, s), 8.39 (1H, d, J = 5Hz) / $CDCl_3$.

(0060)

Example 7

4-(2-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] ethinyl} phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound number 41)

A liquid mixture of 1.30 g of 4-(2-phenyl iodide)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole, 10 ml triethylamine, 4 ml pyridine, 56 mg copper iodide, 104 mg dichlorobis (triphenylphosphine) palladium and 780 mg triphenylphosphine was stirred overnight at 70°C. The reaction liquor was filtered, thereafter concentrated and the residue was refined by silica gel column chromatography and crystallised from hexane - ethyl acetate. The 1.22 g of the title compound thereby obtained as a beige powder represented a yield of 68 %. The NMR data of this compound was as follows.

2.25-2.47 (4H, m), 2.33 (3H, s), 2.38 (3H, s), 3.42 (2H, brs), 3.79 (2H, brs), 7.30-7.58 (17H, m) / DMSO.

(0061)

Example 8

4-(2-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] ethyl} phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound number 41)

Using 700 mg of 10 % palladium-carbon as catalyst, 1.09 g of 4-(2-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] ethinyl} phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole was subjected to a catalytic reduction in 30 ml methanol for three days. The reaction liquor was filtered, and thereafter the residue was refined by silica gel column chromatography and crystallised from hexane - ethyl acetate. The 1750 mg of the title compound thereby obtained as a white powder represented a yield of 67 %. The NMR data of this compound was as follows.

2.20-2.65 (8H, m), 2.23 (3H, s), 2.30 (3H, s), 3.41 (2H, brs), 3.75 (2H, brs), 6.93 (2H, d, J = 7.8Hz), 7.17-7.56 (15H, m) / DMSO.

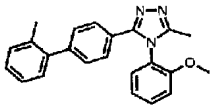
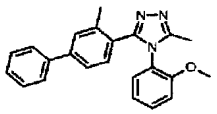
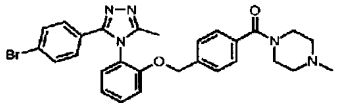
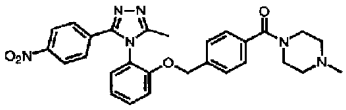
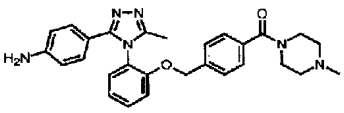
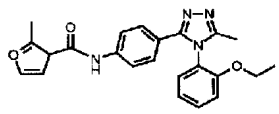
(0062)

The structural formulae of compounds representative of the novel triazole compounds in accordance with this invention including the compounds obtained in the aforesaid Examples, are shown in following Tables 1-16 together with the physical properties thereof. Moreover, for some compounds other than the compounds described in the Examples, these being mainly compounds for which the

physical properties are described as amorphous crystals, the NMR data thereof are also shown in Tables 17-23. Moreover compounds other than the compounds described in the Examples can be readily produced by procedures almost the same as in the aforesaid processes for production and methods in accordance with the Examples, or by applying slight modifications readily apparent to a person skilled in the art to these said methods.

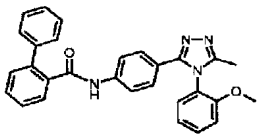
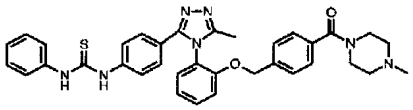
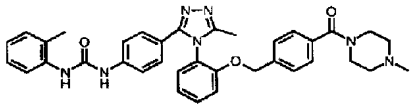
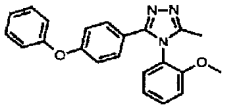
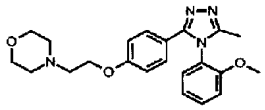
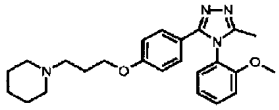
(0063)

Table 1

Comp. No.	Physical properties (mp. °C)	Structural formula
1	161-163	
2	170-172	 tumarate
3	Amorph.	
4	Amorph.	
5	Amorph.	
6	204-206	

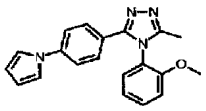
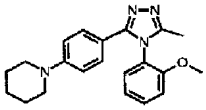
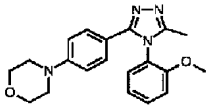
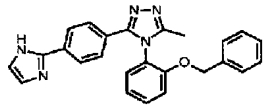
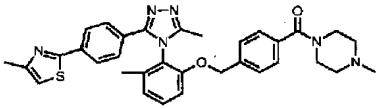
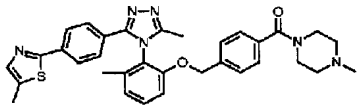
(0064)

Table 2

Comp. No.	Physical properties (mp. °C)	Structural formula
7	241-242	
8	Amorph.	
9	Amorph.	
10	149-150	
11	157-159	
12	Amorph.	

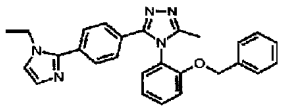
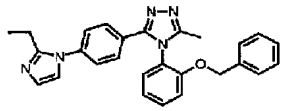
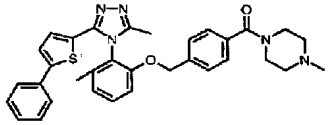
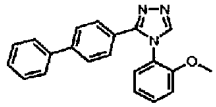
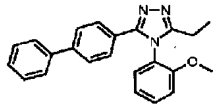
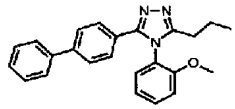
(0065)

Table 3

Comp. No.	Physical properties (mp. °C)	Structural formula
13	181-183	
14	125-126	
15	190-192	
16	185-187	
17	Amorph.	
18	Amorph.	

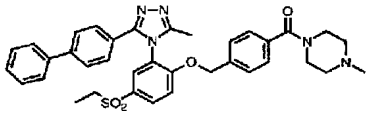
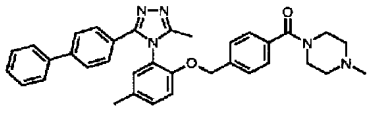
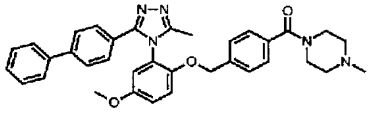
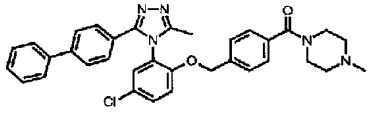
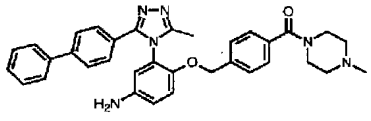
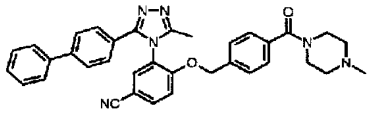
(0066)

Table 4

Comp. No.	Physical properties (mp. °C)	Structural formula
19	196-198	
20	Amorph.	
21	Amorph.	
22	205-207	
23	122-123	
24	145-146	

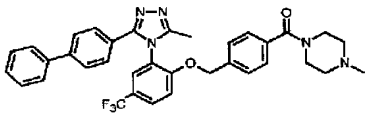
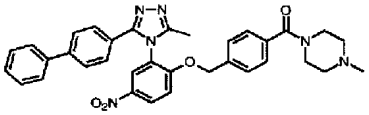
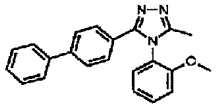
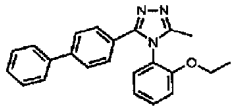
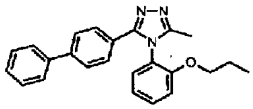
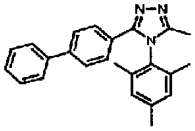
(0067)

Table 5

Comp. No.	Physical property (mp °C)	Structural formula
25	117-119	
26	181-183	
27	89-91	
28	100-102	
29	215-218	
30	167-169	

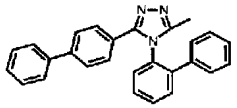
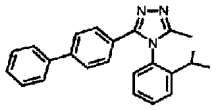
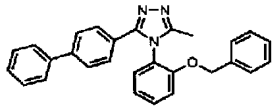
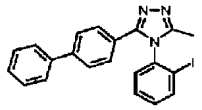
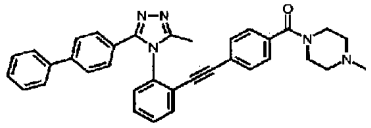
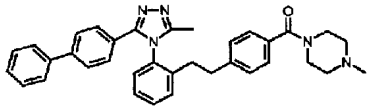
(0068)

Table 6

Comp. No.	Physical property (mp °C)	Structural formula
31	117-120	
32	136-138	
33	183-184	
34	153-155	
35	111-112	
36	125-127	

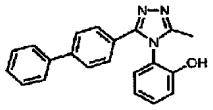
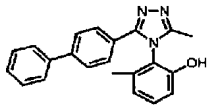
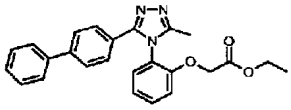
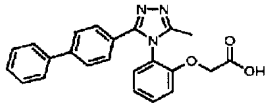
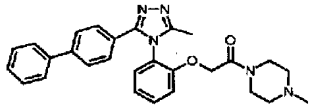
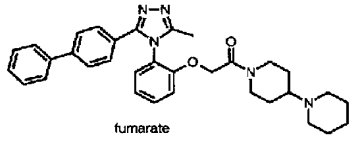
(0069)

Table 7

Comp. No.	Physical property (mp °C)	Structural formula
37	190-191	
38	164-165	
39	171-172	
40	203-205	
41	128-130	
42	92-95	

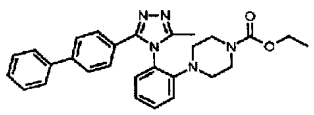
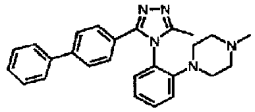
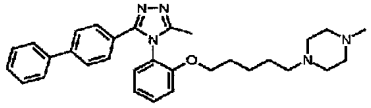
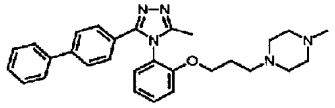
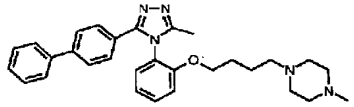
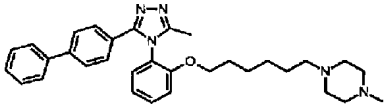
(0070)

Table 8

Comp. No.	Physical property (mp °C)	Structural formula
43	>300	
44	263-265	
45	134-136	
46	154-164	
47	178-180	
48	Amorph.	 fumarate

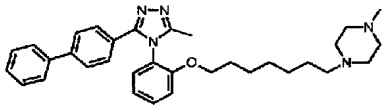
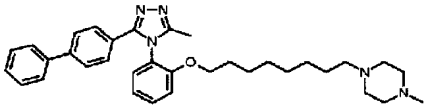
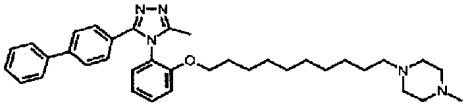
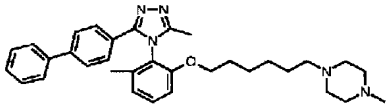
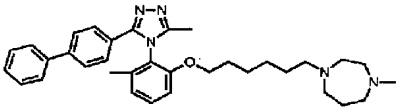
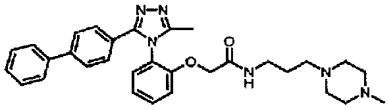
(0071)

Table 9

Comp. No.	Physical property (mp °C)	Structural formula
49	204-206	
50	98-99	
51	115-116	
52	127-128	
53	103-104	
54	96-97	

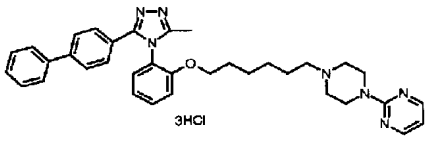
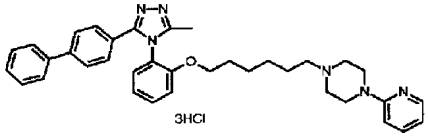
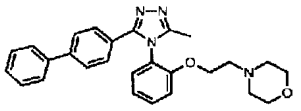
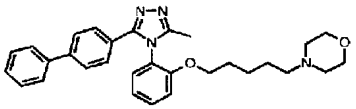
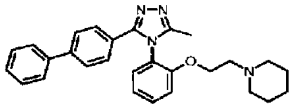
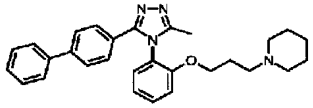
(0072)

Table 10

Comp. No.	Physical property (mp °C)	Structural formula
55	67-68	
56	70-71	
57	87-88	
58	Amorph.	
59	Amorph.	
60	Amorph.	

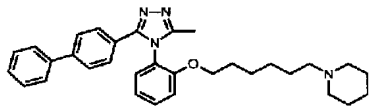
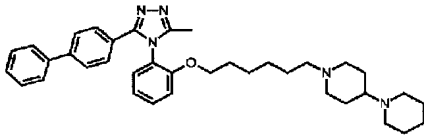
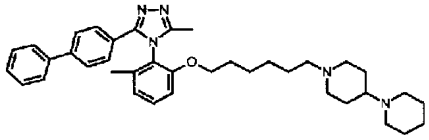
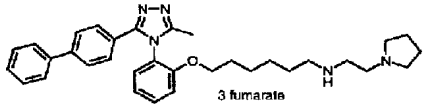
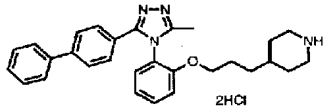
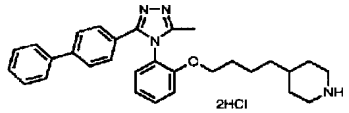
(0073)

Table 11

Comp. No.	Physical property (mp °C)	Structural formula
61	Amorph.	 3HCl
62	Amorph.	 3HCl
63	137-139	
64	80-82	
65	107-108	
66	104-105	

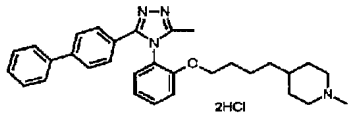
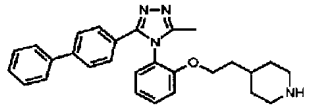
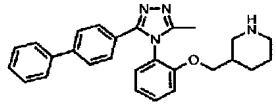
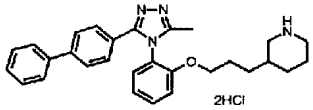
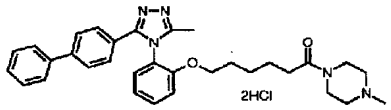
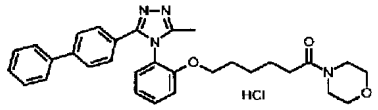
(0074)

Table 12

Comp. No.	Physical property (mp °C)	Structural formula
67	79-81	
68	90-91	
69	98-100	
70	73-73	 3 fumarate
71	Amorph.	 2HCl
72	Amorph.	 2HCl

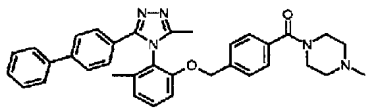
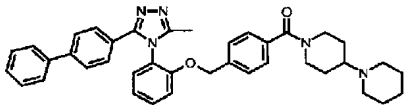
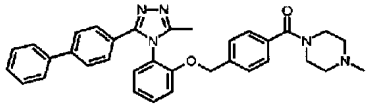
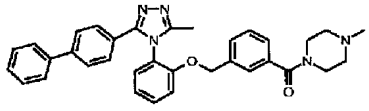
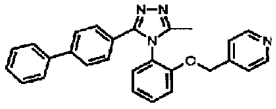
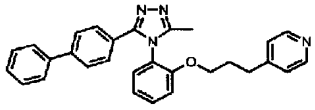
(0075)

Table 13

Comp. No.	Physical property (mp °C)	Structural formula
73	Amorph.	
74	—	
75	Amorph.	
76	Amorph.	
77	Amorph.	
78	Amorph.	

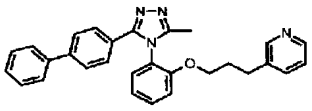
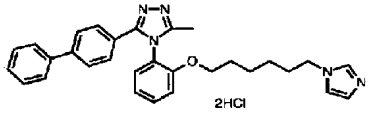
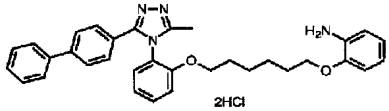
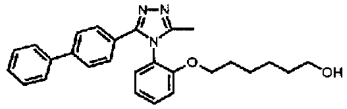
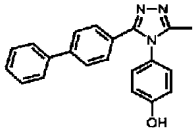
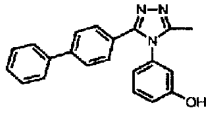
(0076)

Table 14

Comp. No.	Physical property (mp °C)	Structural formula
79	161-164	
80	147-150	
81	179-180	
82	82-84	
83	—	
84	—	

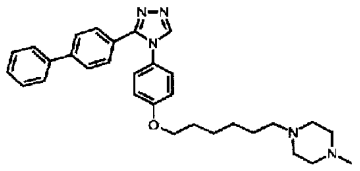
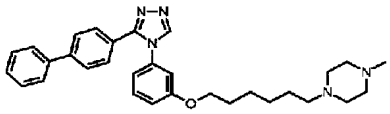
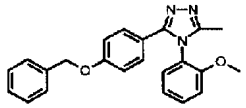
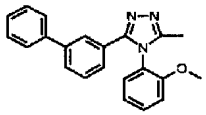
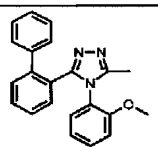
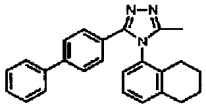
(0077)

Table 15

Comp. No.	Physical property (mp °C)	Structural formula
85	—	
86	80-82	
87	Amorph.	
88	Oil	
89	290-292	
90	277-279	

(0078)

Table 16

Comp. No.	Physical property (mp °C)	Structural formula
91	124-125	
92	85-87	
93	157-158	
94	112-113	
95	142-143	
96	148-150	

(0079)

Table 17

化合物番号	^{1}H−NMR δ (ppm)
3	2.14(3H, s), 2.31(3H, s), 2.46(2H, br s), 3.42(2H, br s), 3.79(2H, br s), 4.93-5.06(2H, m), 7.00-7.05(3H, m), 7.10(1H, dt, J=7.8, 1.0 Hz), 7.21(1H, dd, J=7.8, 1.9Hz), 7.31(3H, t, J=8.8Hz), 7.39(2H, dd, J=6.9, 1.9Hz), 7.48(1H, m)/$CDCl_3$
4	2.33(6H, s), 2.49(2H, br s), 3.41(2H, br s), 3.79(2H, br s), 4.93-5.06(2H, m), 7.06(2H, d, J=8.3Hz), 7.11-7.17(2H, m), 7.23(1H, m), 7.32(2H, d, J=10.3Hz), 7.52(1H, m), 7.60-7.63(2H, m), 8.11(2H, d, J=9.3Hz)/$CDCl_3$
5	2.27(3H, s), 2.32(3H, s), 2.47(2H, br s), 3.41(2H, br s), 3.79(4H, br s), 4.94-5.06(2H, m), 6.50-6.52(2H, m), 7.00-7.07(4H, m), 7.18-7.21(3H, m), 7.31(2H, d, J=8.3Hz), 7.43(1H, m)/$CDCl_3$
8	1.66(3H, s), 2.25(3H, s), 2.32(3H, s), 2.45(2H, br s), 3.39(2H, br s), 3.75(2H, br s), 4.93-5.03(2H, m), 7.00-7.19(4H, m), 7.22(1H, m), 7.26-7.37(7H, m), 7.48(1H, m), 7.81(1H, br s), 7.91(1H, br s)/$CDCl_3$
9	1.64(3H, s), 2.23(3H, s), 2.28(3H, s), 2.32(2H, br s), 2.44(2H, br s), 3.37(1H, br s), 3.77(1H, br s), 4.90-4.98(2H, m), 7.00-7.09(5H, m), 7.11-7.25(9H, m), 7.26(1H, m), 7.43(1H, m), 7.56(1H, br s), 7.71(1H, d, J=7.6Hz), 8.62(1H, br s)/$CDCl_3$

(0080)

Table 18

1 2 fumarate	1. 30-1. 70(6H, m), 1. 90-2. 05(2H, m), 2. 12(3H, s), 2. 40-2. 80(6H, m), 3. 70(3H, s), 8. 90-4. 05(2H, m), 6. 54(2H, s), 6. 75-7. 55(8H, m)/DMSO-d_6
1 7	1. 95(3H, s), 2. 26(3H, s), 2. 31(3H, s), 2. 48(3H, s), 3. 38(2H, br s), 3. 76(2H, br s), 5. 03(2H, m), 6. 89(1H, d, J=0. 9Hz), 6. 92-7. 00(2H, m), 7. 10(2H, d, J=6. 9Hz), 7. 26-7. 44(3H, m), 7. 51(2H, m), 7. 82(2H, dd, J=6. 9, 2. 0Hz)/$CDCl_3$
1 8	1. 95(3H, s), 2. 26(3H, s), 2. 31(3H, s), 2. 45(2H, br s), 2. 74(3H, s), 3. 38(2H, br s), 3. 76(2H, br s), 4. 98-5. 08(2H, m), 6. 91 7. 00(2H, m), 7. 04(2H, d, J=8. 3Hz), 7. 28-7. 37(4H, m), 7. 48(2H, dd, J=6. 9, 1. 9Hz), 7. 77(2H, dd, J=6. 9, 1. 9Hz)/$CDCl_3$
2 0	1. 22(3H, t, J=7. 4Hz), 2. 31(3H, s), 2. 62(2H, q, J=7. 8Hz), 4. 97-5. 10(2H, m), 6. 96(1H, d, J=0. 9Hz), 7. 00-7. 29(8H, m), 7. 33-7. 38(3H, m), 7. 47-7. 55(3H, m)/$CDCl_3$
2 1	2. 05(3H, s), 2. 27(3H, s), 2. 32(3H, s), 2. 43(2H, br s), 3. 36(2H, br s), 3. 75(2H, br s), 5. 05(2H, m), 6. 80(1H, d, J=3. 9Hz), 6. 88(1H, d, J=7. 9Hz), 7. 03(1H, d, J=7. 9Hz), 7. 08-7. 11(3H, m), 7. 26-7. 44(6H, m), 7. 50-7. 53(2H, m)/$CDCl_3$

(0081)

Table 19

4 8 fumarate	1. 25-1. 90(10H, m), 2. 24(3H, s), 2. 45-3. 00(5H, m), 3. 65-3. 80(2H, m), 4. 30-4. 40(2H, m), 4. 92(1H, d, J =15Hz), 5. 04(1H, d, J=15Hz), 6. 56(2H, s), 7. 00-7. 70(13H, m)/DMSO-d_6
5 1	1. 01-1. 12(2H, m), 1. 16-1. 29(2H, m), 1. 37-1. 48 (2H, m), 2. 04-2. 21(10H, m), 2. 10(3H, s), 2. 16(3H, s), 3. 81-4. 01(2H, m), 7. 12(1H, t, J=7. 7Hz), 7. 27(1H, d, J=8. 1Hz), 7. 34-7. 56(7H, m), 7. 63-7. 67(4H, m)
5 5	1. 20(6H, brs), 1. 36-1. 44(2H, m), 1. 50-1. 57(2H, m), 2. 24-2. 30(4H, m), 2. 28 (3H, s), 2. 29(3H, s), 2. 43(6H, brs), 3. 80-3. 87(1H, m), 3. 90-3. 98(1H, m), 7. 02-7. 06(2H, m), 7. 16(1H, dd, J=1. 8Hz, 8. 1Hz), 7. 31-7. 56(10H, m)/$CDCl_3$
5 8	1. 15-1. 20(6H, m), 1. 47-1. 67(4H, m), 1. 91-2. 00(2H, m), 1. 99(3H, s), 2. 25(3H, s), 2. 83(3H, s), 3. 03(1H, brs), 3. 40-3. 70(4H, m), 3. 98-4. 07(3H, m), 7. 06(1H, d, J=7. 8Hz), 7. 19(1H, d, J=8. 7Hz), 7. 37-7. 54(6H, m), 7. 69-7. 75(4H, m)/DMSO
5 9	1. 13-1. 18(4H, m), 1. 51-1. 60(4H, m), 1. 96(3H, s), 2. 14(2H, brs), 2. 26(3H, s), 2. 77(3H, s), 2. 98(2H, brs), 3. 18-3. 77(8H, m), 7. 06(1H, d, J=7. 5Hz), 7. 18(1H, d, J=8. 4Hz), 7. 36-7. 53(13H, m), 11. 40-11. 55(1H, m), 11. 66-11. 84(1H, m)/DMSO

(0082)

Table 20

6 0	1.53(2H, quint, J=7.0Hz), 2.19(2H, t, J=7.0Hz), 2.24-2.42(8H, m), 2.25(3H, s), 2.33(3H, s), 3.12(2H, quart, J=7.0Hz), 4.25(1H, d, J=14.6Hz), 4.37(1H, d, J=14.6Hz), 5.80(1H, t , J=7.0Hz), 6.99(1H, brd , J=8.4Hz), 7.23(1H, brd, J=7.8Hz), 7.32-7.58(11H, m)/$CDCl_3$
6 1 3HCl	0.90-1.20(6H, m), 1.25-1.70(2H, m), 2.40(3H, s), 2.75-3.00(4H, m), 3.20-3.55(4H, m), 3.80-4.05(2H, m), 4.50-4.65(2H, m), 6.70-6.80(1H, m), 7.10-7.80(13H, m), 8.80-8.45(2H, m), 11.41(1H, br)/DMSO-d_6
6 2 3HCl	0.90-1.20(6H, m), 1.25-1.70(2H, m), 2.36(3H, s), 2.80-3.20(4H, m), 3.40-3.75(4H, m), 3.80-4.05(2H, m), 4.35-4.55(2H, m), 6.69-8.15(17H, m)/DMSO-d_6
6 8	1.16-1.22(4H, m), 1.36-1.46(4H, m), 1.52-1.60(8H, m), 1.71-1.85(4H, m), 2.16-2.21(3H, m), 2.29(3H, m), 2.48(4H, brt, J=5.3Hz), 2.85-2.95(2H, m), 3.80-3.87(1H, m), 3.91-3.98(1H, m), 7.02-7.06(2H, m), 7.16(1H, dd, J=1.7Hz, 8.0Hz), 7.31-7.56(10H, m)/$CDCl_3$
7 1 2HCl	0.90-1.75(9H, m), 2.30(3H, s), 2.50-2.75(2H, m), 3.00-3.15(2H, m), 3.80-4.05(2H, m), 7.10-7.80(13H, m), 8.79(1H, br), 9.02(1H, br)/DMSO-d_6

(0083)

Table 21

7 3 2HCl	0.90-1.80(11H, m), 2.31(3H, s), 2.64(3H, s), 2.55-2.95(2H, m), 3.20-3.45(2H, m), 3.75-4.05(2H, m), 7.10-7.80(13H, m), 10.34(1H, br)/DMSO-d_6
7 4	0.95-1.55(7H, m), 2.29(3H, s), 2.35-2.55(2H, s), 2.90-3.00(2H, m), 3.85-4.05(2H, m), 7.07(1H, t, J=7Hz), 7.10-7.60(12H, m)/$CDCl_3$
7 5	0.95-1.80(5H, m), 2.15-2.30(1H, m), 2.28(3H, s), 2.45-2.50(1H, m), 2.30-2.95(2H, m), 3.70-3.85(2H, m), 7.00-7.60(13H, m)/$CDCl_3$
7 6 2HCl	0.80-1.25(3H, m), 1.30-1.75(6H, m), 2.34(3H, s), 2.25-2.80(2H, m), 3.00-3.15(2H, m), 3.85-4.05(2H, m), 7.15-7.85(13H, m), 8.79(1H, br), 9.02(1H, br)/DMSO-d_6
8 0	1.44-1.60(8H, m), 1.75-1.97(2H, m), 1.99(3H, s), 2.26(3H, s), 2.51(5H, brs), 2.66-2.91(2H, m), 3.70(1H, brs), 4.71(1H, brs), 5.02(1H, d, J=12.6Hz), 5.09(1H, d, J=12.6Hz), 6.92(1H, d, J=8.1Hz), 6.97(1H, d, J=7.2Hz), 7.08(2H, J=8.1Hz), 7.25-7.57(12H, m)/$CDCl_3$
8 1	2.27-2.43(4H, m), 2.29(3H, s), 2.32(3H, s), 3.35(2H, brs), 3.75(2H, brs), 4.95(1H, d, J=12.5Hz), 5.06(1H, d, J=12.5Hz), 7.02-7.14(4H, m), 7.24-7.57(13H, m)/$CDCl_3$

(0084)

Table 22

8 2	2. 28-2. 46(4H, m), 2. 29(3H, s), 2. 31(3H, s), 3. 35(2H, brs), 3. 75(2H, brs), 4. 95(1H, d, J=12. 0Hz), 5. 05(1H, d, J=12. 0Hz), 7. 01(1H, d, J=6. 6Hz), 7. 10(2H, t, J=9. 0Hz), 7. 22-7. 58(14H, m)/$CDCl_3$
8 3	2. 34(3H, s), 4. 91(1H, d, J=14 Hz), 5. 05(1H, d, J=14Hz), 6. 84(1H, d, J=5Hz), 6. 96(1H, d, J=8Hz), 7. 10-7. 60(14H, m), 8. 45(1H, t, J=5Hz)/$CDCl_3$
8 4	1. 70-1. 90(2H, m), 2. 32(3H, s), 2. 34-2. 52(2H, m), 3. 70-3. 95(2H, m), 6. 87(1H, d, J=5Hz), 6. 98(1H, d, J=8Hz), 7. 11(1H, t, J=7Hz), 7. 30-7. 60(14H, m), 8. 38(1H, t, J=5Hz)/$CDCl_3$
8 5	1. 75-1. 95(2H, m), 2. 32(3H, s), 2. 30-2. 60(2H, m), 3. 75-4. 00(2H, m), 6. 95-7. 60(15H, m), 8. 30(1H, s), 8. 39(1H, d, J=5Hz)/$CDCl_3$
8 7 2HCl	1. 05-1. 70(8H, m), 2. 35(3H, s), 3. 85-4. 05(2H, m), 6. 95-7. 75(17H, m)/DMSO-d_6
8 8	1. 10(8H, m), 2. 30(3H, s), 3. 54(2H, t, J=6Hz), 3. 80-4. 00(2H, m), 7. 00-7. 60(13H, m)/$CDCl_3$